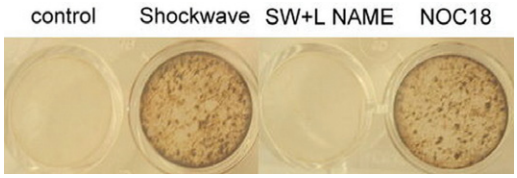

Figure 1

reduced the effects and the results were comparable to the control (Table 1). The addition of NOC18 significantly enhanced the effects of osteogenesis.

Conclusions: The results of the current study tested the hypothesis that ESWT significantly promotes osteogenesis of bone marrow stromal cells. These innovative findings at least in part, explain some of the mechanism of ESWT in hip necrosis.

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EQUIVALENT EFFICACY OF A TOPICAL FORM OF KETOPROFEN (KETUM® 2.5% GEL) AND ORAL DICLOFENAC IN THE TREATMENT OF HAND OSTEOARTHRITIS: RESULTS FROM ARTOPIK STUDY

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Purpose: Hand osteoarthritis (OA) is a common rheumatologic disease, with an estimated prevalence of 38% for women and 24.5% for men, aged over 66 years. The objective of this study is to compare the efficacy and tolerability of a topical form of ketoprofen (Ketum® 2.5% gel) versus oral diclofenac in the treatment of hand OA.

Methods: This randomized, double-blind, double-dummy multicentre clinical trial was conducted in France by 64 general physicians between March 2007 and May 2008. Eligible patients included men and women between 45 and 75 years old, with symptomatic hand OA diagnosed according to the criteria of the American College of Rheumatology and presenting with a base-line visual analogue scale (VAS) score >40 mm and a Dreiser score ≥ 5. Patients were randomly assigned to treatment with ketoprofen gel plus placebo oral capsules, or placebo gel plus oral diclofenac capsules (150 mg/d). Clinical assessments were performed 3 and 7 days after the initiation of the treatment. The primary endpoint was defined as the change of VAS scores (Δ VAS) between base-line and last assessment. The analysis of the primary endpoint in the per-protocol (PP) population was set as the primary analysis. [-8mm to +8mm] was set as the equivalence interval (95% CI). The full analysis set (FAS) and the PP populations were defined a priori in the statistical analysis plan. 61 patients were eliminated from the FAS population (n=395) due, for most of them (46 patients), to compliance issues.

Results: 395 patients, predominantly females (74%), with a mean age of 61 years were included. At base-line, mean VAS score and Dreiser score were 70 mm and 12.5, respectively. Both treatment arms were comparable for all the patients' characteristics. In the FAS population, Δ VAS scores at the end of the treatment [0,4mm to 8,5mm] was slightly outside the equivalence interval. Whereas, in the PP population (n= 334), the result of primary endpoint was [-1,1mm to 7,4mm], demonstrating equivalence of efficacy between Ketum® 2.5% gel and diclofenac per os. Equivalence was also shown for the following secondary efficacy endpoints: Δ VAS scores at 3 days, Δ Dreiser scores at 3 and 7 days, patient efficacy global assessment (PGA) and pain auto-evaluation (see table 1). In terms of tolerability, there was no significant difference between both treatment groups (p=0.108).

Conclusions: This present study shows that, in the PP population, Ketum® 2.5% gel and diclofenac per os are equivalent in terms of efficacy for the treatment of hand OA. These results support that Ketum® could be an alternative therapy to oral NSAID treatments.

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CHALLENGES IN DESIGNING RANDOMIZED CLINICAL TRIALS FOR CARTILAGE REPAIR: THE BST-CarGel EXPERIENCE

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Purpose: To identify and discuss five of the challenges experienced during the designing, planning and execution of a RCT for cartilage repair, using the pivotal study for BST-CarGel® (a new medical device being investigated for the repair of focal articular cartilage lesions) as an example. To summarize some aspects of the trial and of the preclinical work that preceded its design.

Methods: Five major challenges in the process of planning and conducting a pivotal trial for cartilage repair processes were identified and summarized. The preclinical work as the basis to design the trial is summarized. The basics of the currently ongoing international pivotal trial are presented, as well as a brief description of the clinical use of the device.

Results: Major challenges were: Lack of regulatory trial historical comparators for cartilage repair: There were almost no benchmarks when the trial was designed. An FDA guidance was issued only in July 07. Identification of appropriate primary, secondary and tertiary endpoints becomes difficult. Lack of agreement on the appropriate tools to measure outcomes: Pain as primary outcome vs structure of the new tissue. No test presently is the gold standard for cartilage repair; patient relevant tests, designed for OA or ligament reconstruction, based on subjective input are still used.

Abstract 332 – Table 1. Efficacy results

	Ketum® 2.5% gel (*N*=164)	Diclofenac per os (*N*=170)	Statistical analysis
Change of VAS score* at 7 days (mm) (primary endpoint)	-33.2±21.0	-36.9±21.0	[-1.1 ; 7.4] *confidence interval of adjusted difference*
Change of VAS score at 3 days (mm)	-19.7±14.4	-21.3±15.5	0.427 (*P value of ANCOVA*)
Change of Dreiser score** at 7 days	-6.0±4.4	-6.4±4.4	0.190 (*P value of ANCOVA*)
Change of Dreiser score at 3 days	-3.6±3.1	-3.7±3.2	0.568 (*P value of ANCOVA*)
PGA on last assessment	Very efficient: 26.4% Efficient: 36.8% Moderalety efficient: 27.0% Not efficient: 9.8%	Very efficient: 33.5% Efficient: 31.8% Moderalety efficient: 25.9% Not efficient: 8.8%	p=0.304 (*bilateral Wilcoxon test*)
Pain auto-evaluation***	31.2±8.7	29.5±8.9	p=0.078 (*bilateral Wilcoxon test*)
Therapeutic index**** (physician's assessment)	2.86±1.00	3.09±0.97	p=0.033 (*bilateral Wilcoxon test*)

*Score from 0mm (no pain) to 100mm (maximal pain). **Score between 0 (no functional disability) and 30 (maximal functional disability). ***Area under the curve of pain auto-evaluation from day 1 until day 7. ****Ratio of efficacy/tolerability, comprised between 0,25 (worst ratio) and 4 (best ratio).

Biopsy analysis could be an ideal outcome but is sometimes neglected by patients and review ethical boards; the use of advanced MRI techniques as surrogate (T2 and dGEMRIC) is proposed. Difficulties to screen and determine eligibility of appropriate patients: Preoperatory diagnosis of focal cartilage lesions is difficult; until an arthroscopy is performed there's no certainty about the nature of the lesion, as well as of concomitant pathologies. Potential problems arising from concomitant surgeries (ACL reconstructions, multiple lesions) could become confounding factors. Patient enrolment is a true challenge. Standardization of treatment: A high degree of compliance with standardization of actions before, during and after the surgical procedure is difficult to obtain, especially especially for an international trial. Physiotherapy is a critical point and a consensus regarding this aspect of cartilage repair has not been achieved. Need to design a trial which meets expectations of third party payers: Due to needs in terms of regulatory and statistical compliance the indications have to be limited (size/depth of the treated lesions, symptoms, patient age range), or the number of patients needed to demonstrate if there are statistical differences among groups will increase. Difficulty to show potential clinical benefit in the long term is another issue (12 months vs longer and more costly trials). Third party payers are expecting evidence that there's a long lasting improvement. A 12 month interim analysis is being conducted on a subset of 41 patients after 1 year postop. A similar analysis at 6 months suggested evidence of a positive effect of BST-CarGel® on cartilage quantity/quality by MRI compared to control group. No major safety issues occurred.

Conclusions: Trials for study of cartilage repair represent a true challenge for basic researchers, clinicians, industry and for regulatory bodies. This study represents an important step toward developing evidence-based treatment algorithms for cartilage repair as well as for the identification of the diverse hurdles that those trials may represent. It also shows that the use of new tissue structure as a primary endpoint, relying on advanced MRI techniques is feasible.

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INCIDENCE AND SEVERITY OF GASTROINTESTINAL TREATMENT-EMERGENT ADVERSE EVENTS IN PATIENTS TREATED WITH TAPENTADOL EXTENDED RELEASE (ER) OR OXYCODONE CONTROLLED RELEASE (CR) FOR RELIEF OF CHRONIC OSTEOARTHRITIS KNEE PAIN

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Purpose: To characterize the incidence and severity of gastrointestinal (GI) treatment-emergent adverse events (TEAEs) associated with analgesic treatment with tapentadol ER or oxycodone CR in patients with moderate to severe chronic osteoarthritis knee pain.

Methods: In a randomized, double-blind, 15-week phase 3 trial, patients with moderate to severe chronic osteoarthritis knee pain received controlled, adjustable bid doses of tapentadol ER (100-250 mg), oxycodone HCl CR (20-50 mg), or placebo over a 12-week maintenance period, preceded by a 3-week titration period to establish an optimal therapeutic dose. Efficacy was assessed using the change from baseline in average pain intensity over the 12-week maintenance period using the last observation carried forward to impute missing values. The incidence and severity of TEAEs were monitored over the 15-week treatment period.

Results: The intent-to-treat population included 1,023 patients. Compared with placebo, tapentadol ER and oxycodone CR significantly reduced average pain intensity over the 12-week maintenance period (least squares mean difference from placebo [standard error of the mean]: tapentadol ER, -0.7 [0.17], $P<0.001$; oxycodone CR, -0.3 [0.17], $P=0.049$). The overall incidence of TEAEs was 61.1%, 75.9%, and 87.4% in the placebo, tapentadol ER, and oxycodone CR groups, respectively. The incidence of GI TEAEs was 26.1% in the placebo group, 43.0% in the tapentadol ER group, and 67.3% in the oxycodone CR group. Most TEAEs were of mild to moderate intensity. Patients in the tapentadol ER group reported lower incidences of GI TEAEs of moderate and severe intensity than patients in the oxycodone CR group (**Table**). GI TEAEs led to study discontinuation in 1.8% of the placebo group, 7.3% of the tapentadol ER group, and 26.9% of the oxycodone CR group.

Conclusions: Tapentadol ER (100-250 mg bid) was associated with numerically lower incidences of both moderate and severe GI TEAEs and GI TEAEs leading to discontinuation compared with oxycodone HCl CR (20-50 mg bid).

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FUNCTION, PAIN AND THE MODIFYING EFFECTS OF REGIONAL ADIPOSITY AND STRENGTH IN OLDER ADULTS WITH KNEE OA

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Purpose: The purposes of the study were: (1) to examine the relationship of regional adiposity with knee extensor strength, pain, and physical function in older adults with knee osteoarthritis (OA); (2) to investigate the association of knee extensor strength with chair rise time, pain, and physical function; and (3) to explore the relationship of leg extensor power with chair rise time and 4-meter walking speed.

Methods: 34 older adults with knee OA (65% female, mean age = 71 yrs) were enrolled in the Strength Training in ARthritis Trial (START) pilot study. Knee extensor strength was measured for the most affected limb using a Kin-Com 125E Isokinetic Dynamometer set at a speed of 30 deg/s. Leg extensor power (work done per unit time) was assessed using a Nottingham Power Rig. Measures of regional adiposity, percent lower extremity and trunk fat, were obtained via a DXA scan. Chair rise time and 4-meter walking

Abstract 334 – Table 1. Incidence and Severity of Selected Gastrointestinal TEAEs

TEAE, n (%)	Placebo (n=337)			Tapentadol ER (n=344)			Oxycodone CR (n=342)		
	Mild	Moderate	Severe	Mild	Moderate	Severe	Mild	Moderate	Severe
All Gastrointestinal TEAEs	50 (56.8)	33 (37.5)	5 (5.7)	82 (55.4)	55 (37.2)	11 (7.4)	97 (42.2)	114 (49.6)	19 (8.3)
Nausea	14 (60.9)	7 (30.4)	2 (8.7)	48 (64.9)	21 (28.4)	5 (6.8)	59 (47.2)	54 (43.2)	12 (9.6)
Vomiting	4 (36.4)	4 (36.4)	3 (27.3)	11 (61.1)	6 (33.3)	1 (5.6)	28 (45.9)	30 (49.2)	3 (4.9)
Constipation	11 (50.0)	11 (50.0)	0	40 (61.6)	23 (35.4)	2 (3.1)	65 (51.6)	54 (42.9)	7 (5.6)

TEAE, treatment-emergent adverse event; ER, extended release; CR, controlled release.